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ORIGINAL ARTICLE

Radioiodine therapy (RAI) for Graves' disease (GD) and the effect on ophthalmopathy: a systematic review*

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Summary

Background An association between radioiodine therapy (RAI) for Graves' disease (GD) and the development or worsening of Graves' ophthalmopathy (GO) is widely quoted but there has been no systematic review of the evidence.

Aims We undertook a systematic review of randomized controlled trials (RCTs) to assess whether RAI for GD is associated with increased risk of ophthalmopathy compared with antithyroid drugs (ATDs) or surgery. We also assessed the efficacy of glucocorticoid prophylaxis in the prevention of occurrence or progression of ophthalmopathy, when used with RAI.

Methods We identified RCTs regardless of language or publication status by searching six databases and trial registries. Dual, blinded data abstraction and quality assessment were undertaken. Random effects meta-analyses were used to combine the study data. Ten RCTs involving 1136 patients permitted 13 comparisons. Two RCTs compared RAI with ATD. Two RCTs compared RAI with thyroidectomy. Four RCTs compared the use of adjunctive ATD with RAI *vs.* RAI. Five RCTs examined the use of glucocorticoid prophylaxis with RAI.

Results RAI was associated with an increased risk of ophthalmopathy compared with ATD [relative risk (RR) 4·23; 95% confidence interval (CI): 2·04–8·77] but compared with thyroidectomy, there was no statistically significant increased risk (RR 1·59, 95% CI 0·89–2·81). The risk of severe GO was also increased with RAI compared with ATD (RR 4·35; 95% CI 1·28–14·73). Prednisolone prophylaxis for RAI was highly effective in preventing the progression of GO in patients with pre-existing GO (RR 0·03; 95% CI 0·00–0·24). The use of adjunctive ATD with RAI was not associated with any significant benefit on the course of GO.

Conclusion RAI for GD is associated with a small but definite increased risk of development or worsening of Graves' ophthalmopathy compared with ATDs. Steroid prophylaxis is beneficial for patients with pre-existing GO.

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Introduction

Radioiodine therapy (RAI) has been used in the treatment of Graves' disease (GD) for more than six decades but the association between RAI and developing or worsening of Graves' ophthalmopathy (GO) remains unclear. Several retrospective studies reported an association.[1–4] However, others[5–8] did not find a link. A recent questionnaire-based survey carried out by European Group on Graves' Orbitopathy (EUGOGO)[9] found most responders used antithyroid drug (ATD) treatment as first-line therapy for Graves' hyperthyroidism if GO was present; however, after 6 months, if GO was still active, about 80% suggested the thyroid should be ablated. The negative attitude towards RAI has probably changed from the previous 1996 survey.[10] Glucocorticoid prophylaxis is thought to be beneficial when used along with RAI, but routine use in all patients undergoing RAI is considered unnecessary by experts.[11]

Although individual randomized controlled trials (RCTs) have suggested an increased risk of progression of ophthalmopathy after RAI, there has been no systematic review of the evidence. We have undertaken the first systematic review of RCTs to assess whether RAI for GD is associated with increased risk of occurrence or progression of ophthalmopathy, compared with ATD or surgery. We also assessed the role of glucocorticoid prophylaxis and adjunctive ATD in the prevention of occurrence or progression of ophthalmopathy, when used along with RAI.

Methods

Search strategy for identification of studies

We identified studies regardless of language or publication status by searching the Cochrane Central Register of Controlled Trials (CENTRAL issue 3, 2006), MEDLINE (1966 to August 2006), EMBASE (1980 to August 2006), BIOSIS (1985 to August 2006), CINAHL (1982 to August 2006), HEALTHSTAR (1975 to August 2006) and trial registries. We contacted authors of published trials, where appropriate, for further information.

Selection

We included all published and unpublished, randomized and quasi-RCTs of patients of any age receiving RAI for GD, where GD had been adequately defined (diffuse goitre, presence of thyroid

antibodies and/or uniform uptake on isotope scanning). We prespecified a minimum, mean or median follow-up of 1 year from the time of RAI for prespecified outcomes. We sought all RCTs of RAI. We prespecified the comparisons of RAI *vs.* ATD; RAI *vs.* surgery; RAI with adjunctive ATD *vs.* RAI without adjunctive ATD, and RAI with prophylactic glucocorticoids *vs.* RAI without glucocorticoids. Main outcome measures sought were the occurrence of ophthalmopathy after RAI in patients with no pre-existing ophthalmopathy or progression of ophthalmopathy in patients with pre-existing ophthalmopathy, and the incidence of severe ophthalmopathy (need for systemic steroids, immunosuppression, orbital radiotherapy, orbital decompression and visual loss). Additional outcome measures were hypothyroidism and adverse events.

Quality assessment

Quality assessment of RCTs included allocation concealment, whether intention-to-treat analysis was undertaken, comparability of groups at baseline and blinding of outcome assessors.

Data abstraction

Two reviewers independently abstracted data and assessed methodological quality of the studies. Any differences were resolved by discussion between reviewers.

Quantitative data analysis

We used Revman Manager software version 4·2 from the Cochrane collaboration for data analysis. Where appropriate, the results of comparable groups of trials were combined for relative risks (RRs) using random effects models in view of study heterogeneity. Results are presented with 95% confidence intervals (CIs). Heterogeneity between comparable trials was assessed by the I^2 statistic.[12] Prespecified subgroup analyses for smoking and hypothyroidism were planned. Grading of ophthalmopathy was based on clinical activity score (CAS)[13] or similar classification system.

Results

Out of 22 eligible RCTs, 10 RCTs[14–23] described ophthalmopathy outcomes and were included in this review (Fig. 1).

Ophthalmopathy outcomes

Six RCTs systematically evaluated eye outcomes after RAI with ophthalmopathy as a primary outcome. Quality of ophthalmopathy description was heterogeneous in these trials. Four trials assessed ophthalmopathy as a secondary outcome without mentioning the methodology used but described the eye outcome such as severe ophthalmopathy requiring immunosuppression. All trials excluded

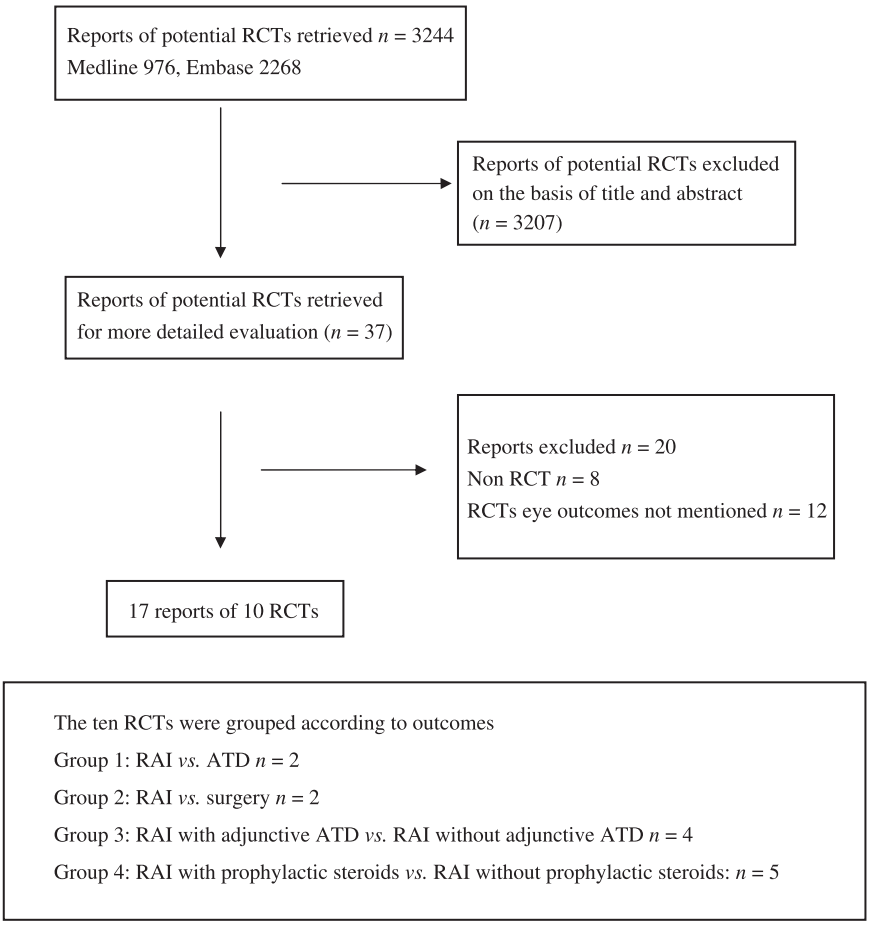

Fig. 1 Trial flow.

Table 1. The characteristics of the RCTs included in the systematic review

Author	Intervention	Duration of follow-up (mean)	Patients enrolled/ assessed at close of study	Description of eye outcome	Methodological rating for concealment of allocation	ATD regime (Block & replace or titration)	RAI dose (Mean SDs) MBq
Tallstedt 1992, Sweden	RAI *vs.* ATD *vs.* surgery	24 months	179 enrolled for 2 groups, 168 completed study. Only group 2 with RAI considered. RAI 39/ATD 38/Surgery 37 assessed	Ophthalmopathy index score	A	Block and replace	Calculated to deliver 120 Gy to thyroid tissue
Bartalena 1998, Italy	RAI *vs.* ATD RAI *vs.* RAI with prednisolone	12 months	450 enrolled, 7 lost to follow-up. RAI 150/ATD 148/RAI with steroids 145	Clinical activity score	B	Titration regime	407 ± 112/ 444 ± 136
Marcocci 1989, Italy	RAI *vs.* RAI with prednisolone	18 months	56 enrolled, 4 lost to follow-up. RAI 26/RAI with steroids 26	Ophthalmopathy index score	A	–	355/363
Vázquez-Chávez 1992, Mexico	RAI *vs.* surgery	49·6 months	40 randomized, RAI 20/ surgery 20	Exophthalmometer	B	–	676
Vaisman 1997, Brazil	RAI *vs.* RAI with prednisolone	18 months	49 randomized, RAI 25/ RAI with steroids 24	Exophthalmometer CT/USD	B	–	187/187
Kung* 1994, Hong Kong	RAI *vs.* RAI with adjunctive ATD (MMI + LT4)	24 months	120 enrolled, 4 lost to follow-up and 2 excluded RAI 57/RAI with ATD57	ATA classification	B		234 ± 139/ 188 ± 112
Gamstedt 1986, Sweden	RAI *vs.* RAI with adjunctive ATD *vs.* RAI with betamethasone	12 months	60 randomized, RAI 23/ RAI with ATD 17/RAI with betamethasone 20	Not mentioned	B	Pretreatment and posttreatment with MMI, T4 added to correct hypothyroidism	350/350
Gamstedt 1991, Sweden	RAI with placebo *vs.* RAI with betamethasone	12 months	40 randomized, RAI 20/ RAI with betamethasone 20	Not mentioned	B	–	350/350
Andrade 2004, Brazil	RAI *vs.* RAI with pre treatment with methimazole	12 months	68 enrolled, 5 lost to follow-up, 2 withdrawn RAI 32/RAI with ATD29	Not mentioned	B	Pretreatment with MMI	287 ± 154/ 241 ± 124
Kung* 1995, Hong Kong	RAI *vs.* RAI with adjunctive ATD (MMI + LT4)	4·6 years	164 enrolled, 5 lost to follow-up. RAI 79/RAI with ATD80	Not mentioned	B	Block and replace	208 ± 117/ 202 ± 103

RAI, radioiodine; ATD, antithyroid drug; MMI, methimazole; LT4, levothyroxine
Methodological rating for concealment allocation: A, method did not allow disclosure of assignment; B, small, but possible chance of disclosure of assignment, or states 'random' but no description; C, quasi-randomized (alternate allocation to groups).
*Personal communication with the author confirms that both RCTs were different with no overlapping of study subjects.

patients with severe ophthalmopathy and enrolled patients with either absent or mild to moderate ophthalmopathy. The outcome on pre-existing eye disease (although mild) was defined in only 5 out of 10 RCTs. No participant lost vision permanently in any RCT (see Table 1 for details).

RAI vs. *ATD*. Two RCTs compared RAI with ATD. Ophthalmopathy developed in 36 out of 189 patients who received RAI compared with 8 out of 186 patients who received ATD. RAI therapy was associated with increased risk of developing or worsening ophthalmopathy compared with ATD (RR 4·23; 95% CI 2·04–8·77) (Fig. 2).

Risk of severe ophthalmopathy. Compared with ATD, RAI was associated with increased risk of severe ophthalmopathy (defined as ophthalmopathy requiring immunosuppression, orbital radiotherapy and/or decompression). Fourteen patients out of 189 in the RAI group developed severe ophthalmopathy compared with 3 patients out of 186 in the ATD group (RR 4·35; 95% CI 1·28–14·73) (Fig. 2).

RAI vs. *thyroidectomy*. Two RCTs compared RAI against thyroidectomy. RAI therapy was associated with slightly increased risk of ophthalmopathy compared with surgery although statistically nonsignificant. Ophthalmopathy developed or progressed in 22 patients out of 59 in the RAI group compared with 13 patients out of 57 who underwent thyroidectomy (RR 1·59; 95% CI 0·89–2·81).

RAI vs. *RAI with adjunctive ATD*. Four RCTs assessed the effects of adjunctive ATD with RAI on ophthalmopathy. Pre-existing eye disease was specified in only one trial by Kung *et al.*[22] Combining

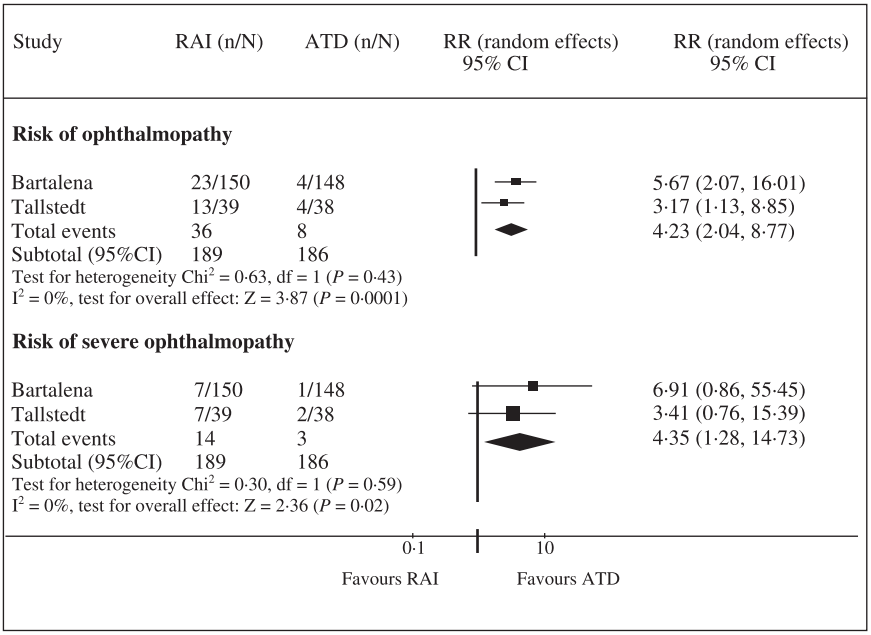

Fig. 2 Radioiodine *vs.* antithyroid drugs. Outcome: Development or worsening of ophthalmopathy.

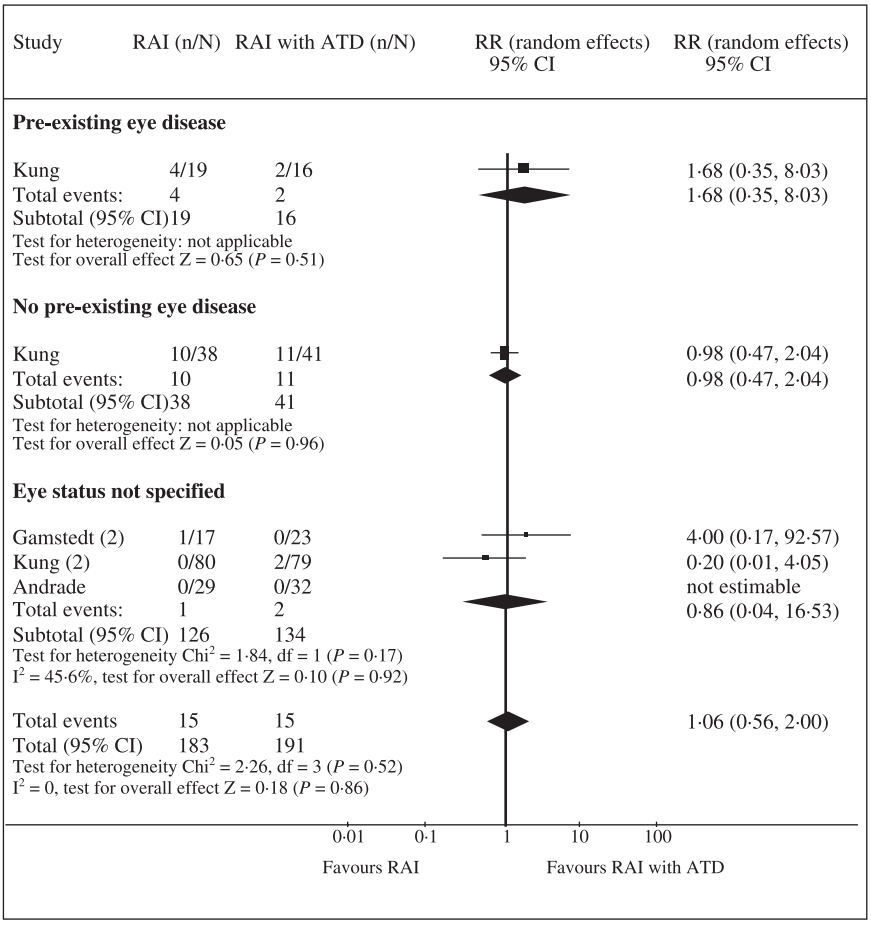

Fig. 3 Radioiodine *vs.* radioiodine with adjunctive antithyroid drug. Outcome: Development or worsening of ophthalmopathy.

these trials showed no significant difference in the ophthalmopathy outcome. Fifteen patients out of 183 in the RAI group developed or worsened GO compared with 15 out of 191 patients in the adjunctive ATD group (RR 1·06; 95% CI 0·56–2·0) (Fig. 3).

RAI with glucocorticoid prophylaxis vs. RAI without glucocorticoid prophylaxis. Three RCTs used prednisolone (0·5 mg/kg body weight/day for 1 month following RAI and then tapered over 2 months) with ophthalmopathy as a primary outcome. Two RCTs used betamethasone

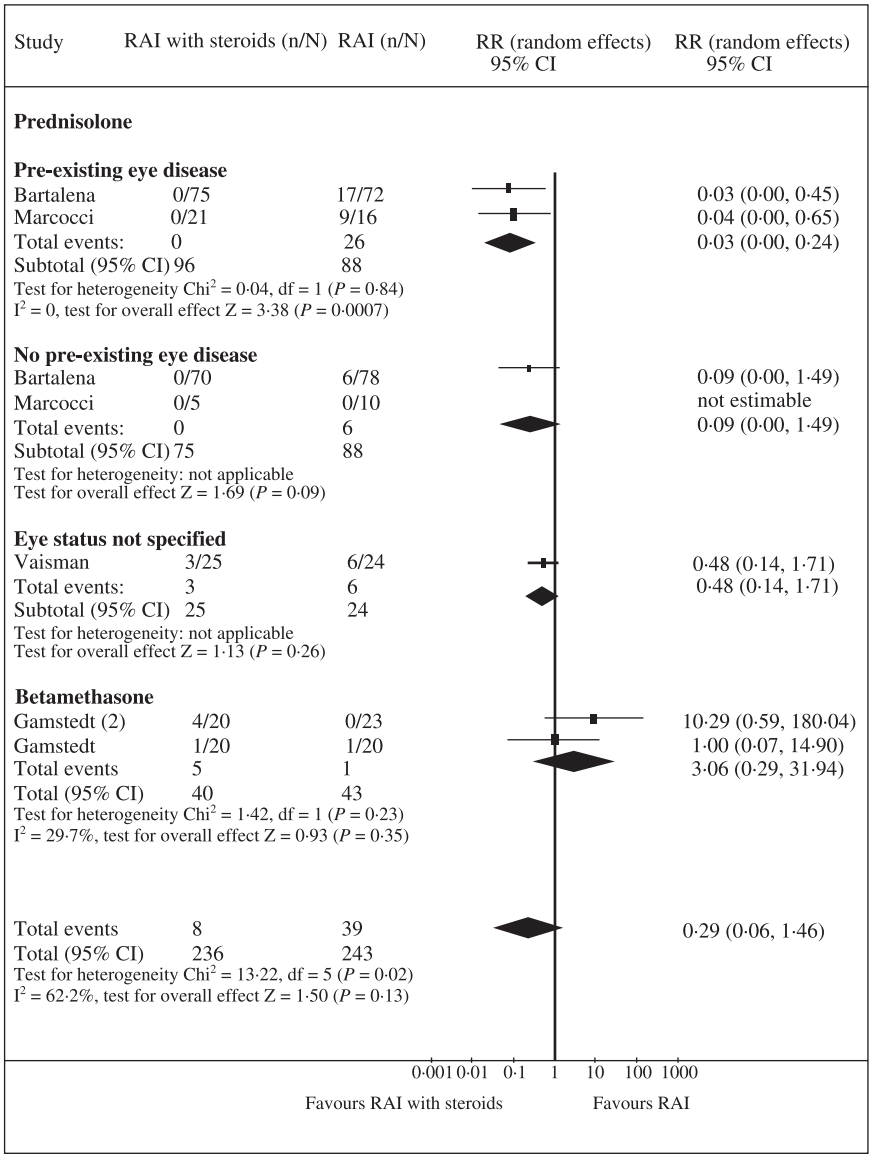

Fig. 4 Radioiodine with prophylactic steroids *vs*. RAI without prophylactics steroids. Outcome: Development or worsening of ophthalmopathy.

for 7 weeks (6 mg/day for 5 days and then tapered weekly by 1·5–0·5 mg. Patients underwent RAI therapy 3 weeks after betamethasone was commenced and were receiving betamethasone 3 mg daily).

Prednisolone prophylaxis was highly effective in preventing worsening of eye disease in patients with pre-existing ophthalmopathy compared with RAI therapy without prednisolone. Ophthalmopathy worsened in 26 patients out of 88 patients with pre-existing eye disease who received RAI alone. None of the 96 patients with pre-existing eye disease who received prednisolone prophylaxis developed worsening of GO (RR 0·03; 95% CI 0·00–0·24). In patients with no pre-existing eye disease, GO developed in 6 out of 88 patients in the RAI group compared with none in the prednisolone group of 75 patients. However, this did not reach statistical significance (RR = 0·09; 95% CI 0·00–1·49). Similarly, there was no significant difference in the eye outcome when steroid prophylaxis was given to patients, where eye status was not predefined (3 out of 25 in steroid prophylaxis *vs*. 6 out of 24 in RAI group, RR 0·48; 95% CI 0·14–1·71) (Fig. 4).

Additional outcomes. Among the studies that reported adverse events, 9% (20 of 231) participants on methimazole developed rashes, including one participant developing a systemic lupus erythematosus type reaction and one with transient neutropenia. No significant side-effects were observed due to systemic steroid therapy apart from transient 'Cushingoid features' in one trial.[19] One participant with known hypertension died due to cerebral haemorrhage while on betamethasone.[16] The incidence of reported atrial fibrillation and heart failure appeared to be low in the trial participants (3 patients out of 1136 participants).

Hyperthyroid cure rate. A full description regarding hyperthyroid cure rate was not available. Although some RCTs mentioned prevalence of thyroid dysfunction at the end of the study, we were unable to undertake a meta-analysis on thyroid status and ophthalmopathy due to lack of full details.

Health related quality of life in patients with GO. No data were available on health related quality of life outcomes in patients with

GO except in one RCT by Tallstedt *et al.*[18,24,25] Long-term follow-up data in these patients showed diminished vital and mental quality of life aspects compared with a reference population, but there were no significant differences among the treatment modalities. For many patients, GO affected life seriously and for 20% of patients GO was more troublesome than GD itself.[25]

Factors influencing the outcome on ophthalmopathy

A pretreatment serum T3 level of ≥ 5 nmol/l [(1·1–2·5nmo1/1)] was associated with increased risk of developing or worsening ophthalmopathy after RAI therapy compared with levels < 5 nmol/l (RR 5·8; 95% CI 1·5.to 22 8) in an RCT by Tallstedt *et al* .[18] Similarly, risk of ophthalmopathy was increased among patients treated with ATD or surgery who had pretreatment serum T3 levels of ≥ 5 nmol/l (RR 12·7; 95% CI 1·7–92·7) compared with T3 levels of < 5 nmol/l. However, overall risk of developing or worsening ophthalmopathy was higher in the RAI group. Kung *et al.* reported no correlation between serum T3, T4 levels and ophthalmopathy.[22] Two RCTs[20,22] reported no correlation between thyroid antibodies/TSH receptor antibodies and GO. Post treatment hypothyroidism (both raised TSH and low T4) was positively associated with ophthalmopathy in one RCT by Kung *et al.*[22] The trial by Bartalena and colleagues described a positive correlation with smoking and GO.[19] There were insufficient data to undertake any subgroup analyses on these factors. Four RCTs mentioned the peak incidence of GO at 6 months after RAI but GO developed at any time after RAI (1–24 months).

Discussion

The natural history of GO is variable but tends to follow 'Rundle's curve', with an early progressive phase of deterioration followed by a plateau lasting for months to years.[26] This is followed by slow improvement but disease severity may not return to baseline. Normalization of thyroid function is considered essential to reduce severity and improve outcomes in GO.[27] A small but significant proportion of patients (5%)[27] experience severe GO that is extremely unpleasant, painful, cosmetically distressing and even sight threatening.[28] Urgent specialist evaluation and interventions such as intravenous glucocorticoids,[29,30] orbital decompression and/or orbital radiotherapy may be required to save vision. Our review shows that compared with ATD, RAI is associated with increased risk of severe GO. Although the absolute risk is small, this cannot be ignored. In this review, 24 patients developed severe GO of which 20 patients were treated with RAI. Eleven patients had pre-existing eye disease and three patients had no pre-existing GO in the RAI group (data were not available in the rest of the patients). Patients with severe GO were treated with immunosuppressive doses of steroids and 16 patients required additional orbital radiotherapy. Five patients also required cosmetic correction. No patient lost sight due to severe GO.

In patients with pre-existing mild GO, prednisolone prophylaxis was highly effective in preventing the progression of GO. No participant in the prednisolone arm of trials developed severe ophthalmopathy. In fact, in some patients with pre-existing ophthalmopathy, the use of prednisolone was associated with some improvement in GO, despite RAI. In patients without any clinical signs of pre-existing GO, or in patients where eye disease was not pre-specified, prednisolone prophylaxis appears to be of limited benefit and routine use following RAI is probably not justifiable. The use of adjunctive ATD with RAI does not prevent adverse eye outcomes.

The pathogenesis of GO is unclear but appears to be an autoimmune-mediated inflammation of extra-ocular muscles and peri-orbital connective tissue. Immunogenic cross reactivity of sensitized T lymphocytes and/or antibodies against common antigens to both thyroid and orbit, such as the TSH receptor and novel protein G2s have been postulated.[31] Following RAI, radiation injury may result in release of such common antigens and precipitate GO. Several other factors, such as smoking, have been found to be associated with GO after RAI, although the exact mechanism is unknown and may be related to direct irritative and/or immune mediated effects.[32,33] Recent work by Cawood *et al.* suggests that smoke might act by increasing adipogenesis in the orbit, and be synergistic with IL–1 in this regard.[34] A meta-analysis of smoking and thyroid disorders by Vestergaard *et al.* showed the odds ratio (OR) for ever smoking with GO was 4·40 (95% CI 2·88–6·73) and was higher than OR for smoking with GD (1·90; CI 1·40–2·55) in six studies.[35] In this review, three RCTs[14,18,19] mentioned a high smoking prevalence (40–60%). Two studies[18,19] described a positive association with smoking and GO but the association was statistically significant in only one study.[19] We could not perform a sub group analysis of smoking and GO after RAI due to the lack of details provided in the trials. Tallstedt *et al.* found a significantly increased risk of developing or worsening of GO in patients with pretreatment serum T3 levels of ≥ 5 nmol/l. However, high serum T3 levels possibly reflect severe immunological disturbance accompanying GD that may predispose to GO rather than be a direct causal effect. There was no correlation with TSH receptor antibody levels and progression of ophthalmopathy observed in these RCTs. However, a recent study by Eckstein *et al.* suggests that a high TSH-receptor antibody titre is an independent risk factor for GO outcome.[36]

Untreated hypothyroidism following RAI is thought to be an important risk factor for developing GO[37] and a recent observational study by Perros *et al.* shows that deterioration of GO in patients with mild GO might be prevented by early administration of T4 following RAI (2 weeks).[38] However, we found no RCT that compared the use of early T4 supplementation *vs.* routine T4 supplementation following RAI.

Although this review aimed to provide definite answers for clinicians, it has several limitations. The methodology used to describe GO is heterogeneous and shows the need for an internationally agreed classification that is clinically useful and reproducible. Most studies have excluded patients with moderate to severe ophthalmopathy suggesting that RAI is avoided in these patients. Although studies have compared RAI against ATD or surgery, in general, studies have used more than one method of treatment to control hyperthyroidism. Not all RCTs conducted in patients with GD using RAI systematically evaluated eye outcomes after RAI[39] and existing evidence comes from a limited number of studies.

Opinion is divided amongst endocrinologists on whether RAI is associated with GO and our systematic review confirms RAI for GD is associated with a small but definitely increased risk of occurrence or progression of GO compared with ATD/surgery. Clinicians should

Table 2. Clinical practice points

Radioiodine therapy for Graves' disease is associated with increased risk of occurrence or progression of ophthalmopathy compared with antithyroid drugs.
The risk of developing new ophthalmopathy or worsening of pre-existing ophthalmopathy is around 20% after radioiodine and around 5% after antithyroid drugs.
The risk of developing severe ophthalmopathy after radioiodine therapy is around 7%.
Smoking, high levels of pretreatment serum T3 (twice the upper limit of normal) and post radioiodine hypothyroidism are associated with increased risk of ophthalmopathy.
A high TSH-receptor antibody titre is an independent risk factor for the progression of ophthalmopathy.
Post radioiodine hypothyroidism should be treated promptly.
In patients with mild pre-existing ophthalmopathy, prednisolone prophylaxis is effective in preventing deterioration.
Routine use of prophylactic steroids with radioiodine therapy is not indicated at present but should be considered in patients at higher risk of eye complications (e.g. smokers).

be aware of this risk and counsel appropriately (see Table 2 for Clinical Practice Points). We also recommend a minimum specialist follow-up of 12 months following RAI since, in most cases, GO develops or worsens at around 6 months. In patients with mild pre-existing GO, prednisolone prophylaxis is highly effective in preventing the progression of GO and should be standard practice. However, until more evidence is available, routine use in all patients undergoing RAI may not be advisable except, perhaps, in those with higher risk, such as smokers.

Acknowledgements

SA, AA and PA were involved in protocol development, searching for trials, quality assessment of trials, data abstraction and data analysis. SP was involved in quality assessment of trials and data abstraction. JB and JSB provided clinical input. PA was involved in resolution of any differences. SA prepared the draft and all the authors have contributed and edited where necessary. No ethical approval was necessary.

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